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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/873,409	06/05/2001	Markus H. Frank	81994/279322	1825

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EXAMINER
YU, MISOOK

ART UNIT	PAPER NUMBER
1642	13

DATE MAILED: 10/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/873,409	FRANK ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,8 and 10-40* is/are pending in the application.

4a) Of the above claim(s) *1-4,8 and 10-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Examiner of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Examiner Misook Yu.

Claims 1-4, 8, and 10-40 are pending. Claims 1-4, 8, 10-17 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. This examiner notes that applicant wants the non-elected claims to be cancelled in the amendment filed on March 06, 2002. However, claims cannot be cancelled without applicant's explicit instructions.

Claims 18-40, drawn to DNA, vector, host cell are examined on merits.

Claim Objections

The objection of claim 5 **is moot** since applicant cancelled the claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Rejection of claims 5-7, and 9 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is moot** since applicant cancelled claims. The new claims also recite "substantially pure" but the specification at the last sentence of page 6 defines the phrase.

Claims 27-29 corresponding to the cancelled claims 5-7 **are rejected** for the reasons set forth at pages 3 and 4 of the prior Office Action, Paper NO. 7 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant argue that claims 27-29 are directed to individual peptides and it is expected the vast majority would not retain the functional properties of the full length sequence form which the

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peptides are derived. However, this argument is not persuasive because the specification does not teach how to make peptides with vast majority that would not retain functional properties.

Claims 27-29 corresponding to claims 5-7 **are rejected** for the reasons set forth at pages 4 and 5 of the prior Office Action, Paper No. 7 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are interpreted as drawn to a genus of unspecified polynucleotide molecules encoding peptides with various differences in amino acid compositions from SEQ ID NO:1-8. Since the specification does not provide any evidence for even a single species, it is concluded that applicant does not adequately describes the entire genus of instantly claimed polynucleotide molecules.

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New Grounds of Rejections and Objections

Information Disclosure Statement

Both copy and list of the IDS filed on June 17, 2002 is missing and therefore cannot be considered with this Office Action. When the copy and list are supplied, the IDS will be considered in the next office action without further fee.

Claim Objections

Claims 27-29, 39, and 40 are objected to because of the following informalities: claim 27 has a peptide sequence requiring a SEQ ID number. Appropriate correction is required.

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Claim Rejections - 35 USC § 112

Claims 27-29, 39 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 recites "polynucleotide is at least ten amino acids in length" but it is not clear what the metes and bounds are for the phrase.

Claim 27 is confusing and indefinite because it is not clear what is being claimed in the instant claim. Applicant's argument at the paragraph bridging pages 7 and 8 does not help to clarify what is being claimed in claim 27.

Claim Rejections - 35 USC § 101

Claims 18-40 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial utility, and a credible asserted utility or a well established utility. Claims 18-40 are directed to SEQ ID NO:9-16 encoding novel human proteins SEQ ID NO: 1-8, and variants of SEQ ID NO: 9-16 encoding a smaller unspecified peptides with various differences in amino acid compositions from SEQ ID NO:1-8, vectors and host cells.

The specification discloses at pages 3-5 that SEQ ID NO:1-8 are eight different novel human proteins encoded by different exons on human chromosome 7 and also says at page 5 lines 4-11 that cancer multidrug resistance may result from the expression of any of the proteins of SEQ ID NO:1-8. The specification at page 18 lines 1-11 says that structural prediction indicates that SEQ ID NO:1-8 are P-glycoproteins and the proteins have homology to human MDR1 and MDR3. These disclosures are not sufficient to determine what the biological function(s) of each of the proteins SEQ ID NO:1-8 is because Scott et al (Nature Genetics, 1999, 21:440-443) teach that the function of newly identified gene products is unpredictable even when the database searches reveal significant homology to proteins of known function. Scott et al teaches that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter 'downregulated in adenoma'. However, upon analyzing the expression and kinetics of

the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. states that these results underscore the importance of confirming the function of newly identified gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph).

Generally, the art acknowledges that function cannot be predicted based solely on structural predictions (see page18 line 1 of the specification) or similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247:1306-1310) state

that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (p. 1306). Thus, the specification fails to support the asserted credible, specific and substantial utility of the newly identified instantly claimed protein and for the DNA molecule encoding the protein.

The specification, for example, at page 19 lines 8-10 contains assertions that some of the proteins encoded by the instantly claimed invention or some of the instantly claimed DNA molecules could be used as a cancer marker, especially human melanoma. However, the specification does not provide any evidence. Therefore, this examiner could not evaluate whether any of the protein or DNA could be used as cancer marker or not. Further, it is not clear whether any of the proteins expressed in vivo because the specification does not provide any evidence. The specification does not support a credible, specific and substantial utility because the specification does not teach a relationship to any specific disease or establish any involvement of the claimed invention in the etiology of any specific disease or does not teach what the function(s) of the protein is. Also, the specification does not show whether the claimed polynucleotides are overexpressed or underexpressed **in a specific, diseased tissue compared to the healthy tissue control**. It is not clear whether the human melanoma used at page 19 line 9 was cell line or primary human tumors. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, page 4) teaches that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with

representation of malignancy, with characteristics profoundly different from the human disease. Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Thus, since it is not clear whether the expression studies were conducted with culture cells or with primary tumors cells and data were not presented with the specification to be evaluated, the disclosed utilities are not considered specific, credible, and substantial. Disclosure in the instant specification is just invitations for one skilled in the art to figure out how the proteins functions or what the biological activities are for the claimed invention, or indeed they are P-glycoprotein. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to use applicants' alleged discovery, not how to find out how to use it for themselves. The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a credible, specific and substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed protein. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

Claims 18-40 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a either a specific and substantial utility, and a credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu
October 18, 2002

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